REMARKS

Reconsideration of this application is respectfully requested. Claim 1 has been amended for clarification. Claims 1-7 and 9-11 are currently pending.

Examiner Interview Summary

At the outset, applicants wish to thank Examiner Jennifer M. Kim and Supervisory Patent Examiner Brandon Fetterolf for the courtesy and helpful suggestions extended to the inventor, Dr. Marco Pappagallo, and his counsel, Irina Vainberg, during the Examiner interview conducted on January 21, 2010. During the interview, the patentability of the claimed invention over the cited references was discussed. In particular, the cited disclosure in U.S. Patent Application No. 2004/0063670 ("Fox") regarding the method of treating pain was discussed. This prior treatment method was distinguished from the claimed invention by the inventor and his counsel, primarily because the earlier method does not treat chronic spinal mechanical pain, which is a key innovation of the presently claimed invention. It was further explained that Fox's method provides short term relief not prolonged pain relief. In light of the foregoing, the Examiner's agreed that the patient population recited in the pending claims is not taught by Fox. The Examiners suggested that applicants demonstrate that it would not have been obvious to treat chronic pain by applying methods useful for treating acute pain. The Examiners also stated that the patentability of Pamidronate for treating chronic spinal mechanical pain might be favorably considered by the Examiner.

Indefiniteness Rejection

Claims 1-7 and 9-11 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the invention. According to the Examiner, the phrase "the most recent administration of the bisphosphonate" is unclear.

In response, claim 1 has been amended without prejudice or disclaimer to recite "the administration of the bisphosphonate." Accordingly, claims 1-7 and 9-11 are definite, and withdrawal of the indefiniteness rejection is respectfully requested.

Obviousness Rejection

Claims 1-7 and 9-11 have been rejected as obvious over Fox in view of Geusens et al., *J. Clin. Densitometry* (2001), 4(4): 389-394 ("Geusens"). Fox is cited as teaching the administration of pamidronate and zoledronate for treating inflammatory hyperalgesia and mechanical hyperalgesia. The Examiner also cites Fox as disclosing that the bisphosphonate may be administered to a patient, e.g., once daily, once weekly, once every month, once every three months, once every six months, or once a year. The Examiner concedes that Fox fails to teach pain relief for a duration of at least three months following administration of the bisphosponate. Geusens is cited by the Examiner as teaching progressive recovery from back pain following intermittent IV infusions of pamidronate. According to the Examiner, it would have been obvious for one of ordinary skill in the art to administer pamidronate or zoledronate to treat any mechanical or inflammatory pain.

The rejection is traversed, and reconsideration is respectfully requested.

Applicants respectfully submit that the present invention is not obvious over the cited references because, *inter alia*, neither reference teaches or suggests administration of bisphosphonates for prolonged pain relief of chronic spinal mechanical pain.

First, the pending claims relate to a very specific patient population suffering from chronic mechanical back pain. This particular patient population is not disclosed or suggested by Fox. At best, Fox discloses treating inflammatory hyperalgesia and mechanical hyperalgesia - i.e., diseases characterized by increased response to an external stimulus. *See* Fox at paragraphs [0102] - [0108]. Importantly, the hyperalgesia test models disclosed by Fox cannot be applied to chronic mechanical pain because the pain associated with hyperalgesia is an acute response to a painful stimulus, whereas chronic mechanical back pain is a continuous form of pain that persists regardless of

external stimulation. In the Fox reference, for example, hyperalgesia is triggered when rat paw skin is stimulated with a painful stimulus (e.g., pin prick or hot plate). The painful stimulus causes an increased response to pain compared to what would be observed in a normal state. Fox at paragraphs [0102] - [0108]. Accordingly, Fox does not disclose or suggest chronic mechanical back pain because, in contrast to hyperalgesia, chronic mechanical back pain is known to progress even in the absence of painful stimulation or movements.

Further, those of ordinary skill in that art would readily appreciate that methods for treating acute forms of pain are not necessarily applicable to treating chronic pain. It is well established that "chronic pain" relates to pain that is "prolonged" or "long-term." For instance, the U.S. National Center for Health Statistics defines a chronic condition as one of three months' duration or longer. In contrast, "acute pain" is defined as "brief," or "not chronic" pain. *See* STEDMAN'S MEDICAL DICTIONARY 22-23 (Williams & Wilkins, 26th ed. 1995) (copy enclosed as Exhibit A). Chronic pain is associated with functional, structural, and chemical changes in the brain, thus putting it into the realm of a disease state, rather than a protracted "acute symptom." *See* Tracey et al., *J. Pain*, 2009, 10(11): 1113-20 (copy enclosed as Exhibit B).

In view of the foregoing, the patient population targeted by Fox is different from the patient population in the present invention. Further, the Examiner provides no reason as to why a skilled artisan would apply the teachings of Fox to the specific patient population recited in the pending claims.

Moreover, the Examiner acknowledges that Fox fails to teach pain relief for a duration of at least three months following administration of pamidronate and zoledronic acid. *See* Office Action at page 5. Indeed, Fox suggests that bisphosphonates only exhibit a short term effect. *See* Fox at, e.g., paragraph [0102] ("The effect was rapid in onset, with a maximal reversal of 100% within 30 min, and of short duration with no significant activity 3 h following administration."); *see also* paragraph [0108]. Thus Fox provides no teaching which would have led the skilled artisan to administer bisphosphonates for prolonged pain relief of at least three months.

Finally, applicants respectfully submit that the Examiner's reliance on Geusens for disclosing the use of bisphosphonates for treating back pain is a mischaracterization of the reference because Geusens does not teach that bisphosphonate has any direct effect on pain relief. Geusens discloses an individual case study wherein an 18 year old boy was subjected to multiple therapies. The patient in Geusens did have an improvement in his pain, but other treatments he received, alone or in combination, can account for this improvement. In addition to bisphosphonates, the patient in Geusens received irradiation, calcium, vitamin D, calcitonin, physiotherapy, progressive mobilization, glucocorticoids, analgesics, and nonsteroidal anti-inflammatory drugs. *See* Geusens at page 390. Since there were several variables involved in the treatment regimen, long term recovery from pain cannot be directly correlated with administration of the bisphosphonate. Thus, there is no disclosure in Geusens that would have led one of ordinary skill in the art to recognize any association between a bisphosphonate and chronic spinal mechanical pain relief, let alone the particular duration of relief following administration of the bisphosphonate, as called for in the pending claims.

For at least the reasons set forth above, the claims are not obvious over Fox and Geusens. Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered, and that the pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: March 22, 2010

Respectfully submitted,

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EXHIBIT A

STEDMAN'S Medical Dictionary

26th Edition

ILLUSTRATED IN **COLOR**

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ac·ti·va·tor (ak′ti-vā-tōr). **1.** A substance that renders another substance, or catalyst, active, or that accelerates a process or reaction. **2.** The fragment, produced by chemical cleavage of a proactivator, that induces the enzymic activity of another substance. **3.** An apparatus for making substances radioactive; *e.g.*, neutron generator, cyclotron. **4.** A removable type of myofunctional orthodontic appliance that acts as a passive transmitter of force, produced by the function of the activated muscles, to the teeth and alveolar process that are in contact with it.

catabolite gene a. (CGA), SYN catabolite (gene) activator *protein.*

plasminogen a., a proteinase converting plasminogen to plasmin by cleavage of a single (usually Arg-Val) bond in the former. SYN urokinase.

polyclonal a. (pol-ē-klō′năl), a substance that will activate T cells, B cells, or both regardless of their specificities.

tissue plasminogen a. (TPA), thrombolytic serine protease catalyzing the enzymatic conversion of plasminogen to plasmin through the hypolysis of a single Arg-Val bond; a genetically engineered protein used as a thrombolytic agent in patients with thrombotic occlusion of a coronary artery.

ac·tiv·i·ty (ak-tiv′i-tē). **1.** In electroencephalography, the presence of neurogenic electrical energy. **2.** In physical chemistry, an ideal concentration for which the law of mass action will apply perfectly; the ratio of the a. to the true concentration is the a. coefficient (γ), which becomes 1.00 at infinite dilution. **3.** For enzymes, the amount of substrate consumed (or product formed) in a given time under given conditions; turnover *number.*

blocking a., repression or elimination of electrical activity in the brain by the arrival of a sensory stimulus.

insulin-like a. (ILA), a measure of substances, usually in plasma, that exert biologic effects similar to those of insulin in various bioassays; sometimes used as a measure of plasma insulin concentrations; always gives higher values than immunochemical techniques for the measurement of insulin.

intrinsic sympathomimetic a. (ISA), the property of a drug that causes activation of adrenergic receptors so as to produce effects similar to stimulation of the sympathetic nervous system.

nonsuppressible insulin-like a. (NSILA), plasma insulin-like a. not suppressed by antibodies to insulin and mostly present after pancreatectomy. Nonsuppressible insulin-like a. is mostly the action of polypeptide insulin-like growth factors IGF-I and IGF-II.

optical a., the ability of a compound in solution (one possessing no plane of symmetry, usually because of the presence of one or more asymmetric carbon atoms) to rotate the plane of polarized light either clockwise or counterclockwise.

plasma renin a. (PRA), estimation of renin in plasma by measuring the rate of formation of angiotensin I or II.

specific a., (1) radioactivity per unit mass of the stated element or compound; (2) for an enzyme, the amount of substrate consumed (or product formed) in a given time under given conditions per milligram of protein; (3) a. per unit mass of the stated radionuclide.

triggered a., one or a series of spontaneously generated heart beats originating from an action potential that produces an afterdepolarization which reaches activation threshold.

ac·to·my·o·sin (ak′-tō-mī′ō-sin). A protein complex composed of the actin and myosin; it is the essential contractile substance of muscle fiber, active with MgATP.

platelet a., the contractile protein of platelets, responsible for clot retraction, platelet aggregation, and release of ADP and other biologic amines essential to platelet function. SYN thrombosthenin.

Ac·u·a·ria spi·ra·lis (ak-ū-ā′rē-ă spī-rā′lis). A nematode parasite in the proventriculus and esophagus, and sometimes the intestine, of chickens, turkeys, pheasants, and other birds. [L. *acus,* needle; Mod. L. *spiralis,* spiral]

acu·i·ty (ă-kyū′i-tē). Sharpness, clearness, distinctness. [thr. Fr., fr. L. *acuo,* pp. *acutus,* sharpen]

absolute intensity threshold a., the minimal light that can be seen.

resolution a., detection of a target having two or more parts, often measured by using the Snellen test types; indicated by two numbers: the first represents the distance at which an individual sees the test types (usually 6 meters or 20 feet), and the second, the distance at which the test types subtend an angle of 5 minutes; *e.g.,* vision of 6/9 indicates a test distance of 6 meters and recognition of symbols which subtend an angle of 5 minutes at a distance of 9 meters. SYN visual a.

spatial a., detection of the shape of a test object; *e.g.,* perceiving polygons of the same size but with different numbers of sides.

stereoscopic a., the detection of differences in distance by superimposition of slightly different retinal images into a single image to the brain.

Vernier a., detection of displacement of a portion of a line.

visibility a., recognition of an object on a background of different character.

visual a. (V), SYN resolution a.

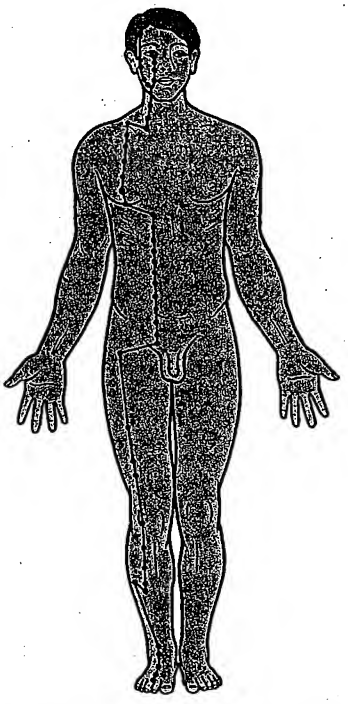
acu·le·ate (ă-kyū′lē-āt). Pointed; covered with sharp spines. [L. *aculeatus,* pointed, fr. *acus,* needle]

acu·mi·nate (ă-kyū′mi-nāt). Pointed; tapering to a point. [L. *acumino,* pp. *-atus,* to sharpen]

ac·u·ol·o·gy (ak-yū-ol′ō-jē). The study of the use of needles for therapeutic purposes, as in acupuncture. [L. *acus,* needle, + G. *logos,* study]

a·cu·pres·sure. Application of pressure in sites used for acupuncture with therapeutic intent.

ac·u·punc·ture (ak-yū-punk′chūr). Puncture with long, fine needles: **1.** An ancient Oriental system of therapy. **2.** More recently, acupuncture *anesthesia* or analgesia. [L. *acus,* needle, + puncture]



acupuncture (stomach meridian (cardinalis stomachi))

acus (ā′kŭs). Rarely used term for needle. [L.]

ac·u·sec·tion (ak′yū-sek-shŭn). Rarely used term for electrosurgery using a needle.

ac·u·sec·tor (ak′yū-sek-ter). Rarely used term for needle used for electrosurgery. [L. *acus,* needle, + *secare,* to cut]

acu·sis (ă-kyū′sis). The ability to perceive sound normally. SYN normal hearing. [G. *akousis,* hearing]

acute (ă-kyūt′). **1.** Referring to a health effect, brief; not chronic;

sometimes loosely used to mean severe. **2.** Referring to exposure, brief, intense, short-term; sometimes specifically referring to brief exposure of high intensity. [L. *acutus,* sharp]

acy·a·not·ic (ă-sī-ă-not′ik). Characterized by absence of cyanosis.

acy·clic (ā-si′klik). Not cyclic; denoting especially an a. compound.

acy·clo·guan·o·sine (ā-sī-klō-gwan′ō-sēn). SYN acyclovir.

acy·clo·vir (ā-sī′klō-vir). A synthetic acyclic purine nucleoside analogue used as an antiviral agent in the treatment of genital herpes; the sodium salt is used for parenteral therapy. SYN acycloguanosine.

ac·yl (as′il). An organic radical derived from an organic acid by the removal of the carboxylic hydroxyl group.

ac·yl-ACP de·hy·dro·gen·ase, ac·yl-ACP re·duc·tase. SYN enoyl-ACP reductase (NADPH).

ac·yl·ad·e·nyl·ate (as′il-ă-den′il-āt). A compound in which an acyl group is combined with AMP by elimination of H_2O between the OH's of a carboxyl group and of the phosphate residue of AMP, usually initially in the form of ATP and eliminating inorganic pyrophosphate in the condensation.

ac·yl·am·i·dase (as-il-am′i-dās). SYN amidase.

***n*-ac·yl·a·mi·no ac·id** (as-il-am′i-nō). RCO–NH–CHR–COOH; an amino acid to the N of which an acyl group is attached, as in hippuric acid (*N*-benzoylglycine) or phenaceturic acid.

ac·yl·a·tion (as-i-lā′shŭn). Introduction of an acyl radical into an organic compound or formation of such a radical within an organic compound.

acylcar·ni·tine (as′il-kar′ni-tēn). Condensation product of a carboxylic acid and carnitine. The transport form for a fatty acid crossing the mitochondrial membrane.

ac·yl-CoA. $RCH_2COSCoA$ or $RCH_2CO{\sim}SCoA$; condensation product of a carboxylic acid and coenzyme A, and metabolic intermediate of importance, notably in the oxidation and synthesis of fat. SYN acyl-coenzyme A.

a.-CoA dehydrogenase (NADPH$^+$), enzyme catalyzing the reversible reduction of enoyl-CoA derivatives of chain length 4 to 16, with NADPH as the hydrogen donor, forming a.-CoA and $NADP^+$. SYN enoyl-CoA reductase.

a.-CoA synthetase, (1) general term for enzymes (EC 6.2.1) that form a.-CoA, now called ligases; **(2)** specifically, long-chain fatty acid–CoA ligase.

ac·yl·co·en·zyme A (as′il-kō-en′zīm). SYN acyl-CoA.

1-ac·yl·gly·ce·rol-3-phos·phate ac·yl·trans·fer·ase. SEE *lysophosphatidic acid* acyltransferase.

ac·yl-mal·o·nyl-ACP syn·thase. SYN 3-oxoacyl-ACP synthase.

ac·yl·mer·cap·tan (as′il-mer-kap′tan). SYN thioester.

***N*-ac·yl·sphin·gol** (as-il-sfing′gol). Obsolete synonym for *N*-acylsphingosine.

***N*-ac·yl·sphin·go·sine** (as-il-sfing′gō-sēn). A condensation product of an organic acid with sphingosine at the amino group of the latter compound.

ac·yl·trans·fer·as·es (as-il-trans′fer-ā-sez) [EC class 2.3]. Enzymes catalyzing the transfer of an acyl group from an acyl-CoA to various acceptors. SYN transacylases.

acys·tia (ā-sis′tē-ă). Congenital absence of the urinary bladder. [G. *a-* priv. + *kystis,* bladder]

A.D. Abbreviation for *auris dexter* [L.], right ear.

ad-. To, toward; increase; adherence; near; very.Prefix denoting increase, adherence, to, toward; increase; adherence; near; very. [L. *ad,* to, toward;]

-ad. In anatomical nomenclature, -ward; toward or in the direction of the part indicated by the main portion of the word. [L. *ad,* to]

ADA Abbreviation for American Dental Association.

ad·a·cr·ya (dak′rē-ă). Absence of tears; tearlessness. [G. *a-* priv. + *dakryon,* tear, + -ia]

adac·ty·lous (ā-dak′tĭ-lŭs). Without fingers or toes.

adac·ty·ly (ā-dak′ti-lē). Congenital condition characterized by the absence of digits (fingers or toes); autosomal recessive in Holstein cattle. [G. *a-* priv. + *daktylos,* digit]

Adair-Koshland-Némethy-Filmer mod·el (AKNF). See under model.

ad·a·man·tine (ad-ă-man′tēn). Exceedingly hard; formerly used in reference to the enamel of the teeth. [G. *adamantinos,* very hard]

ad·a·man·ti·no·ma (ad-ă-man-ti-nō′mă). Obsolete term for ameloblastoma.

a. of long bones, a rare tumor of limb bones, usually the tibia, that microscopically resembles an ameloblastoma; the histogenesis is uncertain.

pituitary a., SYN craniopharyngioma.

Adamkiewicz, Albert, Polish pathologist, 1850–1921. SEE *artery* of Adamkiewicz.

Adams, Robert, Irish physician, 1791–1875. SEE A.-Stokes *disease;* Stokes-A. *disease;* A.-Stokes *syncope, syndrome;* Stokes-A. *syndrome;* Morgagni-A.-Stokes *syndrome.*

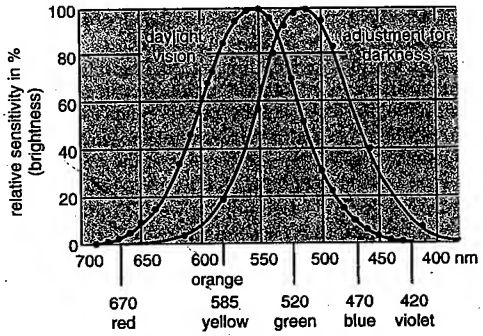
Adams, Sir William, British surgeon, 1760–1829.

Adam's ap·ple. SYN laryngeal *prominence.*

ad·am·site (DM) (ad′ăm-sīt). A vomiting agent that has been used in military training and in riot control. [Roger *Adams,* Am. chemist]

Adanson, Michel, French naturalist, 1727–1806. SEE adansonian *classification.*

ad·ap·ta·tion (ad-ap-tā′shŭn). **1.** Preferential survival of members of a species because of a phenotype that give them an enhanced capacity to withstand the environment including the ecology. **2.** An advantageous change in function or constitution of an organ or tissue to meet new conditions. **3.** Adjustment of the sensitivity of the retina to light intensity. **4.** A property of certain sensory receptors that modifies the response to repeated or continued stimuli at constant intensity. **5.** The fitting, condensing, or contouring of a restorative material, foil, or shell to a tooth or cast so as to be in close contact. **6.** The dynamic process wherein the thoughts, feelings, behavior, and biophysiologic mechanisms of the individual continually change to adjust to a constantly changing environment. SYN adjustment (2). **7.** A homeostatic response. [L. *ad-apto,* pp. *-atus,* to adjust]



dark and light adaptation
brightness of the colors during daytime and twilight

dark a., the visual adjustment occurring under reduced illumination in which the retinal sensitivity to light is increased. SEE ALSO dark-adapted *eye.* SYN scotopic a.

light a., the visual adjustment occurring under increased illumination in which the retinal sensitivity to light is reduced. SEE ALSO light-adapted *eye.* SYN photopic a.

photopic a., SYN light a.

reality a., the ability to adjust to the world as it exists.

retinal a., adjustment to degree of illumination.

scotopic a., SYN dark a.

social a., adjustment to living in accordance with interpersonal, social, and cultural norms.

adapt·er, adap·tor (a-dap′ter, -tōr). **1.** A connecting part, join-

EXHIBIT B

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ELSEVIER

Critical Review

How Neuroimaging Studies Have Challenged Us to Rethink: Is Chronic Pain a Disease?

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Abstract: **In this review, we present data from functional, structural, and molecular imaging studies in patients and animals supporting the notion that it might be time to reconsider chronic pain as a disease. Across a range of chronic pain conditions, similar observations have been made regarding changes in structure and function within the brains of patients. We discuss these observations within the framework of the current definition of a disease.**

Perspective: ***Neuroimaging studies have made a significant scientific impact in the study of pain. Knowledge of nociceptive processing in the noninjured and injured central nervous system has grown considerably over the past 2 decades. This review examines the information from these functional, structural, and molecular studies within the framework of a disease state.***

Key words: *Chronic pain, disease, neuroimaging, central nervous system.*

Editor's Note: This article is 1 in a series of invited Critical Review articles designed to celebrate The Journal of Pain*'s 10th year anniversary of publication.*

Neuroimaging studies have made a huge impact scientifically. The techniques and paradigms are now penetrating the fields of clinical medicine,[65] diagnosis,[12] and even drug discovery.[13,88,103]

The pain field is no exception to these exciting developments, and our knowledge of nociceptive processing in the noninjured and injured central nervous system has grown considerably over the past 2 decades. To date, the focus has been to measure functional correlates of the human pain experience using either blood flow based methods, such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (FMRI), or via electrophysiological methods, such as magnetoencephalography (MEG) and electroencephalography (EEG). Many excellent reviews and several meta-analyses have been written summarizing the findings to date,[1,2,16,99] with more recent reviews focusing on the neural basis of pain modulation and its relief.[10,60,93,100,101] Techniques that focus on the structural architecture of the brain, in terms of gray matter density,[3,4] white matter connections,[8,47] receptor density,[50,56] brain biochemistry,[41,43] and neurotransmitter availability[56,91,105,108] have been applied also to the field of pain with often surprising results.

In this review, rather than regurgitate much of the information already reviewed and current regarding human central pain processing, we want to examine the information from these functional, structural, and molecular studies within the framework of a disease state. This is partly motivated by the observation that treatment options are pharmacologically and behaviorally similar for many patients, despite aetiologies for the pain, particularly when neuropathic, being different.[49,70] This has been taken as evidence that the symptoms likely share some overlapping mechanisms, common to the chronic-pain condition, which the various drugs target irrespective of the cause. Certainly, the focus on mechanism-based analgesic drug development and treatment,[73,106] reinforces this concept that some shared changes occur during the

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transition to a chronic-pain status. The question is whether these changes are detectable using current or advanced techniques, and if so, do the changes that reflect common underlying mechanisms, constitute a diseaselike process.

Why is any of this important? Well, chronic pain is an enormous medical-health problem. Current statistics estimate that approximately 20% of the adult population have chronic pain,[14] and separate to the physical and emotional burden it brings, the financial cost to society is huge, currently estimated at over €200 billion per annum in Europe, and $150 billion per annum in the USA. Treatment options are limited with many patients either not responding or having incomplete pain reduction.[31,71,96] A paradigm shift in our thinking is needed if we are to better diagnose, manage, and treat chronic pain. Certainly beyond the immediate pain community, we need to encourage people to consider chronic pain in a new light and very possibly as a disease in its own right. This review presents the data, but we leave the reader to decide whether sufficient evidence exists to reclassify chronic pain as a disease.

Distinguishing Disease From Syndrome

According to the Compact Oxford English Dictionary (http://www.askoxford.com/), the most common definition of the noun 'disease' is "a disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms." A more expansive definition includes it being a "cause of discomfort or distress" (Oxford English Dictionary). In contrast, the definition of syndrome is "a group of symptoms which consistently occur together." The main distinction here is that in order for something to be a disease there must be an identifiable disorder of structure or function and not just a grouping of symptoms. The factors leading to the disorder of structure or function might vary, as is the case with cancer, but the end result must be a disordered system. In the case of chronic pain, the disorder would be within the nervous system. Historically, chronic pain has been labeled as a syndrome (or group of syndromes), but recent evidence, mainly from neuroimaging studies, strongly suggests that chronic pain could be labeled as a disease.

Disordered Function Producing Discomfort and Distress: Evidence from Functional Imaging

Chronic pain is discomforting and distressing for most patients. Providing objective proof that this is the case, in addition to listening to the patient or examining their behavior, can be obtained using functional imaging. Areas of the brain involved in processing and controlling affect, negative emotions like depression, anxiety, and aversion, are now better understood and include structures like the amygdala, anterior insular cortex, prefrontal cortices, parahippocampal region, amongst others. Recruitment of these regions could be taken as evidence for the patient's pain causing discomfort or distress. For instance, the processing of experimental heat pain in patients with somatoform pain disorder compared to matched controls revealed, despite similar behavioral ratings, a hypoactive state of the ventromedial prefrontal/orbitofrontal cortex (BA 10/11) and a hyperactive state of the parahippocampal gyrus, amygdala, and anterior insular.[45] An earlier study by Gracely et al[40] on fibromyalgia patients showed that pain catastrophizing, independent of depression, was significantly associated with increased activity in similar brain regions, particularly those associated with attention and anticipation to pain, as well as emotional aspects of pain. Interestingly, such findings are found across different patient types supporting common disturbances in function. For instance, in patients with Irritable Bowel Syndrome (IBS), Mayer et al[68] found that compared to patients with ulcerative colitis and control subjects, the IBS group had increased activity in response to rectal distention within the amygdala and prefrontal cortices, amongst other limbic and paralimbic regions. Kulkarni et al found that osteoarthritic knee pain was associated with increased activity in the cingulate cortex, thalamus, and the amygdala when compared to experimental knee pain.[58] Finally, focusing on the neural correlates underpinning the patients' ongoing, tonic pain, Baliki et al[5] again emphasized the relevance of the medial prefrontal cortex, including rostral ACC, during episodes of sustained, high, ongoing pain. Furthermore, its activity was strongly related to the intensity of chronic back pain.

These findings of an altered cerebral processing of either experimentally induced or disease-related pain in patients support previous findings identifying the relevance of these structures in pain anticipation,[15,77,79,80] and anxiety-induced pain amplification.[29,76]

Evidence of disturbed prefrontal activity and a dysfunction of emotion regulation during experimental pain stimulation in depressed patients have been shown in recent studies.[7,95]

Such data forces us to think about how factors associated with chronic pain conditions, like depression, can become part of the overall condition itself and contribute to the discomfort and distress via increased activity within relevant brain regions. For instance, in patients with fibromyalgia, it has been shown that their degree of depression was related to amygdala and anterior insular activity during experimental pain,[38] as well as medial prefrontal cortex activity during disease-relevant induced pain in patients with rheumatoid arthritis and suffering depression.[90]

The anterior insular cortex is particularly intriguing because of its role beyond pain perception. Current thought links activity within the anterior insula to, among other factors, interoception, body awareness, anxiety, depression, fear, and possibly even consciousness.[18-21] There is therefore a potential link to a sense of body disturbance, discomfort, and distress. In a meta-analysis performed by Schweinhardt et al,[89] it was shown that the peak coordinate of activity in clinical pain was shifted to the anterior insular cortex compared to nociceptive pain in healthy volunteers, whose activity was more

midposterior insular. This apparent maladaptive plasticity and shift in brain activity towards the more affective division of the insular cortex is perhaps indicative of a functional disturbance.

One consequence of this discomfort and distress is the impact it has on a patient's cognition,[28] and is perhaps a direct way of confirming the presence of centrally induced alterations in normal cognitive functioning due to pain. While many neuroimaging studies examine the neural basis for how attention and distraction modulate the pain experience, they have largely been done in healthy control subjects and not patients.[101] The reverse has rarely been examined,[93] namely identifying a disruption in normal cognitive brain processing due to the presence of pain, except for 1 study in healthy controls.[11] Studies looking at how pain alters your capacity to make rational decisions due to biases in cost and reward calculations identify, again in healthy subjects, that pain is clearly disruptive to normal cognition,[94] and one can readily extrapolate these findings to testable experiments in patients that might produce further evidence to support functions being disturbed.

In summary, these findings strongly support the case for dysfunctional pain processing, especially in affect-regulating regions, and that these patterns of brain activity strongly reflect patients being in true discomfort and distress.

Disordered Functions and Departure from State of Health: Evidence from Functional Imaging

We shall examine 3 areas where normal physiological functions have been shown to be disturbed in chronic pain states, indicating a departure from a state of health: 1) resting state networks; 2) descending inhibition and facilitation; and 3) thalamic asymmetry.

Resting State Networks

Several years ago, it was observed that subjects undergoing neuroimaging data collection while at rest displayed functional connectivity of specific cortical regions,[32,44] and that this observation was robust across subjects and modalities. These connectivities are now considered as components of the default mode network (DMN), a set of brain regions including medial prefrontal cortex, medial temporal lobes, and posterior cingulate cortex /retropslenial cortex that display balanced positive and negative correlations and are disrupted in several neurological and psychiatric disorders.[22,32,82,84] In response to task performance, certain areas within the DMN reliably deactivate, and in an early study, we found complete abolishment of normal nociceptive-induced deactivation in the capsaicin model of central sensitization in the presence of gabapentin,[54] suggesting a possible interaction with the default mode network. Baliki et al[6] more specifically investigated whether long-term pain alters the functional connectivity of these cortical regions known to be active at rest. During execution of a simple visual task, which patients with chronic back pain performed as well as controls, they found that patients displayed reduced deactivation in several key default-mode network regions. Their findings demonstrate that chronic pain, like other major neurological and psychiatric diseases, has a widespread impact on overall normal brain function.

Descending Inhibition and Facilitation

The descending pain modulatory system is a well-characterized anatomical network that enables us to regulate, largely within the dorsal horn, nociceptive processing in varying circumstances to produce either facilitation or inhibition.[30,48,100] The relevance of descending facilitation in chronic-pain states has gathered considerable momentum over the past few years,[37,78,97] and our human work in models of central sensitization confirm that this facilitatory system becomes active and underpins the maintenance of the centrally sensitized state.[54,59,107] In parallel, many studies in chronic-pain patients have highlighted also a dysfunction in the normal descending inhibition displayed by healthy volunteers, indicating a dysfunction in this powerful and dedicated endogenous pain modulatory system in chronic pain.[9,39,46,63,83,92]

Thalamic Asymmetry

Experimentally induced tonic pain has previously been reported to result in less thalamic activation when compared to acute phasic pain in PET studies.[25] However, controversy exists, as increased blood flow to the thalamus has also been reported and thought to reflect an arousal reaction to pain,[75] and to be involved in the processes of attention and vigilance.[33,81] Evidence from patient studies, however, supports the fact that blood flow to the thalamus is reduced: A common finding has been a relative decrease in thalamic CBF during ongoing pain, which then receded after analgesia and symptom improvement.[26,34,35,52,53,74] Indeed, historically, thalamic infarcts have long been recognized as a cause of spontaneous pain[24] and more recently, atrophy of the thalamus has also been reported in patients with chronic back pain using voxel-based morphometry (see section below).

Therefore, perhaps the most convincing data directly to support the idea that pain is a disease, rather than a syndrome, involves evidence that it is a disorder of structure, as well as function. This is consistent with the definition of disease ("a disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms.")

Disturbed Structure of the Brain: Evidence from Anatomical MRI

In 2004, Apkarian et al[3] reported that chronic-pain patients had less brain gray matter than age-matched control subjects. That study was conducted in chronic low-back pain patients and showed that such patients had reduced gray matter in the thalamus and in the lateral prefrontal cortex, a region involved in descending pain modulation. The gray-matter loss was greater in patients who had neuropathic type symptoms than ones who did not, and the

decrease in gray matter correlated with the duration of the symptoms. Similar studies have now been conducted in patients with chronic headache, fibromyalgia and irritable bowel syndrome (IBS), and chronic regional pain syndrome (CRPS).[66] Although the details of which brain regions show the largest effects differ among studies, gray-matter decreases have been observed in all of these populations.[23,36,57,61,85,86] The predominant gray-matter decreases observed in patients with chronic pain contrast with usage-related increases in brain gray matter that has been observed during learning,[27] and during repeated painful stimulation in healthy subjects.[98] Similarly, patients with cluster headache who show increased hypothalamic activation have increased gray matter in the region of increased activation.[67]

Another anatomical neuroimaging method, diffusion tensor imaging (DTI), allows in vivo mapping of the anatomical connections in the human brain. Hadjipavlou et al[47] used this method to identify anatomical circuitry involved in the top-down influence on pain processing, involving the periaquaductal grey (PAG) and its connections with the prefrontal cortex, amygdala, thalamus, and rostroventral medulla. This method has now been applied to chronic-pain patients, where we see disruptions of structure within brain regions involved in normal modulatory influences on pain.[36,61]

Together, these anatomical studies show that chronic pain is associated with structural changes in the brain. Nevertheless, the current cross-sectional studies tell us little about cause and effect. This is particularly important, since chronic-pain patients frequently have comorbid conditions, including anxiety and mood disorders, altered life-styles so are generally more sedentary, and are also taking various drugs that themselves might be contributing to these measured changes. Thus, it is possible that the gray matter changes are related to the comorbid factors and not to the pain itself. Although some studies have excluded patients with major comorbid conditions such as depression,[57] other studies suggest that such factors are important to the gray-matter changes. For example, Schmidt-Wilcke et al[87] observed that when depression and age were included as nuisance factors, most of the observed gray-matter changes were no longer significant, Similarly, we cannot identify from these neuroimaging studies the cellular basis for changes in grey-matter size—is this a neurodegenerative phenomenon, or are the structural changes related to non-neural cells? In order to answer these questions, animal studies are needed. Animal models are available to address a number of chronic pain conditions, including neuropathic pain, headache, CRPS, arthritis, inflammatory visceral pain conditions, and back pain. On the other hand, such models do not completely mimic functional pain conditions, where the etiology is unknown. Nevertheless, the use of rodents with short life spans will allow us to conduct longitudinal studies lasting only months, but covering a large part of the animal's life span. A recent 5-month longitudinal study of rats undergoing a nerve injury (spared nerve injury—SNI) revealed reductions in the size of frontal cortex, but not until 20 weeks after the injury. Although the rats showed mechanical and thermal hyperalgesia from the time of the injury, they began demonstrating anxiety-like behavior at approximately the same time as the changes in frontal cortex became manifest (Seminowicz et al, in press). Many chronic-pain patients show anxiety-like behavior after their pain has persisted for months or years, so it is interesting to speculate that some of these secondary effects of chronic pain may well be associated with structural changes in the brain.

Rodent studies also allow for histological analysis of the tissue, thus helping us interpret the anatomical changes seen with neuroimaging methods. Metz et al[69] investigated layer 2/3 pyramidal neurons in acute slices of the medial prefrontal cortex (mPFC) in the rat SNI model of neuropathic pain. These investigators found changes in dendritic branching and spine density of the neurons, providing the first direct evidence of anatomical changes at the cellular basis associated with chronic pain.

Neurochemical Disruptions in the Brain: Evidence from PET Studies

Studies are now beginning to show that chronic-pain patients may have altered brain neurochemistry. Using in vivo proton magnetic-resonance spectrometry (^{1}H-MRS), Grachev et al[42] observed altered brain chemistry in the frontal cortices of chronic back-pain patients. Decreased levels of the neuronal marker N-Acetyl aspartate were observed in the dorso-lateral prefrontal cortex, a region in which gray-matter decreases were also observed in back-pain patients. Using similar techniques, Mullins et al[72] showed that glutamate is elevated in the cingulate cortex in response to painful stimuli in healthy humans, and Harris et al[51] showed that reductions in glutamate in the posterior insula in fibromyalgia patients is associated with reduced experimental and clinical pain. These neurochemical findings add further evidence to the idea that reduced gray-matter density in chronic-pain patients may be related to possible excitotoxicity and neuronal loss.

Other studies show possible changes in neurochemicals involved in pain modulation in chronic-pain patients. Two seminal molecular-imaging studies using positron emission tomography (PET) in chronic-pain patients showed cerebral decreases in opioid receptor binding in patients with central neuropathic pain and with rheumatoid arthritis.[55,56] More recent PET studies in fibromyalgia patients show alterations in both dopamine and opioid availability in the forebrain.[50,104] In the absence of external painful stimuli, fibromyalgia patients appear to have a reduction in the receptor availability of both dopamine D2 receptors and opioid mu-receptors in parts of the forebrain. For dopamine, it has also been shown that patients do not release dopamine in the basal ganglia in response to an external pain stimulus, whereas healthy subjects do release dopamine in that situation.[91,105] Such results may mean that patients have decreased receptor availability or have a heightened background tone or endogenous release of these neurotransmitters that is known to produce a reduced phasic release, but in either case, it appears that neurochemicals important for pain modulation are not responding as

they do in healthy individuals. Again, these findings are not specific to fibromyalgia but are shown for other chronic-pain conditions. Willoch et al[102] found in patients with central poststroke pain reduced opioid binding in pain-processing regions and Maarrawi et al[62] showed differential opioid-receptor availability in central and peripheral neuropathic-pain patients. Combined, these studies strongly support the case for disorder or dysfunction in the neurochemistry of chronic-pain patients' brains.

Does the Evidence Prove that Chronic Pain is a Disease?

This review has presented substantial functional, anatomical, and neurochemical evidence that chronic-pain patients have altered brains. But is what we see as altered and dysfunctional central nervous system processing more an adaptive response to the constant nociceptive barrage rather than a diseaselike process? The chicken and egg problem here is that for most "diseases" normally something within the body alters and changes function and possibly structure, and this process itself largely produces the symptoms and condition. For pain, we only have evidence of such changes after the transition to chronicity; therefore, it's difficult to know whether these mechanism-based changes are simply a normal adaptive response or are critical for the chronic-pain state itself. Reversibility of such changes with symptom improvement might help clarify this issue. However, if these changes could be induced without any initiating nociceptive input, would a chronic-pain-like state occur? In many conditions, chronic pain results after a clear tissue-damaging event, leading first to acute pain and then to chronic pain. Most neuropathic pain conditions have a clear nerve injury that precipitated the pain. Nevertheless, other painful conditions come about without a clear precipitating injury. These conditions, such as fibromyalgia, vulvodynia, interstitial cystitis, and irritable bowel syndrome, are sometimes referred to as functional pain syndromes, because the patient presents with pain without an obvious physiological cause. Could these conditions be related to pathophysiology of the central nervous system that is similar to that caused by a constant nocicieptive barrage in other pain conditions? Recent data from animal studies investigating stress-induced hyperalgesia[64] and peripheral hypersensitivity without peripheral inflammation after amygdala activation[17] provide support for this concept. Could an excitotoxicity of pain-modulatory circuitry be evoked not only by hyperexcitability of the afferent nociceptive system, but also, given the right genetic susceptibilitly, by activation of the stress, arousal, or attentional circuitry in humans? At this time, we can only speculate about these mechanisms.

Conclusion

By taking a multifactorial and longitudinal approach to the study of chronic pain, including in our analyses genetic and environmental factors, and merging data from the molecular to the clinical level, we may someday unravel the complexities of chronic pain. But for now, imaging studies have shown that chronic pain is associated with functional, structural, and chemical changes in the brain, thus putting it into the realm of a disease state.

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